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To The TGA Advisory Committee,

The authors of the Australian Paracetamol Project strongly support the up scheduling of modified-release (MR) paracetamol preparations to schedule 4. We suggest also suggest that immediate release (IR) paracetamol in packs of greater than 20 tablets should become Schedule 3.

The Australian Paracetamol Project (APP) is a prospective observational study, that is an arm of the Australian TOxicology Monitoring (ATOM) study.[1, 2] APP recruits patients throughout NSW and QLD from Poison Information Centres and Toxicology units. APP has studied MR paracetamol and massive (> 40g) IR paracetamol overdose. We believe the results from these studies provide evidence for the up scheduling of MR paracetamol and large paracetamol packs.

ATOM-3 describes the clinical characteristics, management and outcomes of MR paracetamol overdose.[2] Importantly it showed following MR overdose the pharmacokinetics are often unpredictable, with delayed and double peak concentrations and prolonged absorption even beyond 24 h. There were high rates of hepatotoxicity despite early acetylcysteine treatment and despite early levels being less than double the nomogram line. Furthermore, treatments such as activated charcoal and increased acetylcysteine did not appear to substantially mitigate the risk of acute liver injury. This lack of mitigation by increased treatment contrasts with observational studies of massive IR overdose, where these treatments decreased the risk of acute liver injury.

The figure below (right side) shows data not published in the ATOM 3 paper, but which was presented at toxicology meetings and the Australasian College for Emergency Medicine, Annual Scientific Meeting. It shows the age distribution of MR overdose in ATOM 3. Of concern is that the largest age group who ingested MR paracetamol in overdose were females under 20 years of age. We believe up scheduling MR paracetamol will decrease access of MR paracetamol to this high-risk age group (who are much less likely to have medical reasons for benefitting from 3 vs 4 doses/day use of paracetamol).

Furthermore, the European Medicines Agency: Pharmacovigilance Risk Assessment Committee (PRAC) recommend suspending the marketing of MR paracetamol in Europe. Importantly this committee found "that the advantages of a longer-acting product did not outweigh the complications of managing an overdose of the medicine." Studies of MR paracetamol for osteoarthritis of the knee and dental pain have shown MR paracetamol was equivalent or non-inferior to IR paracetamol and may be more convenient.[3, 4] Hence we feel MR paracetamol should be schedule 4 due to its risks in overdose.

We also recommend the up scheduling of immediate release (IR) paracetamol in packs of greater than 20 tablets should become Schedule 3. The figure below (left side) was not published in ATOM-2 but, has been presented at toxicology conferences. It shows the age distribution of massive IR overdose. Of concern the largest age group were females under 20 years. We believe that easy access to large (500mg x 100

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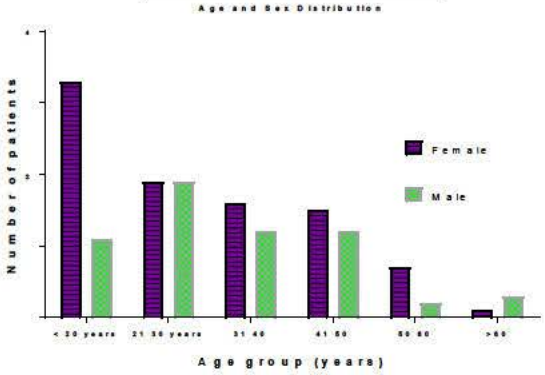
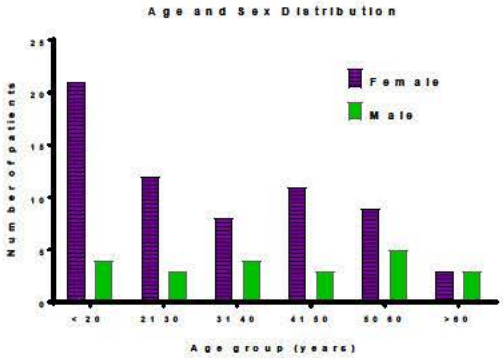
tablets), cheap ($2) packets of paracetamol is a possible reason for this. Large numbers of paracetamol can be easily purchased without the need to speak to a pharmacist. For a recent presentation on paracetamol at the national toxicology conference (TAPNA), I showed how easy it was to buy a large amount of paracetamol. See photo attached, where I purchased 500 paracetamol 500mg tablets for less than $10.

In ATOM 2 (Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose) we demonstrated that patients who ingest "massive" (> 40g) amounts of paracetamol are at risk of hepatotoxicity despite early treatment with acetylcysteine and can have prolonged absorption and persistently high paracetamol concentrations requiring prolonged treatment. Two studies from the UK have demonstrated similar findings with those patients with a higher initial paracetamol concentration have higher rates of acute liver injury, despite early treatment with acetylcysteine. Hence, restricting pack size to young adults and adolescences is extremely important. As patients who take larger overdoses, with higher initial paracetamol concentrations are at increased risk of acute liver injury.

A/ ATOM 2:
Massive IR Overdose



B/ ATOM 3:
MR overdose



A/ Massive (≥ 40 g) immediate release paracetamol overdose: age distribution data

B/ MR paracetamol overdose: age distribution data

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The photos above are from a recent presentation at an Australian Toxicology meeting (May 2018) showing the ease with which very large numbers of paracetamol can be bought.

In summary, the up scheduling of MR paracetamol to schedule 4 and packets > 20 tablets IR to schedule 3, is important to reduce the likelihood of impulsive purchases of dangerous quantities of these products. This would have minimal impact on the older population that might get some benefit from using these larger pack sizes.

Regards

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References:

1. Chiew, A.L., et al., Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2). Clin Toxicol (Phila), 2017. 55(10): p. 1055-1065.

2. Chiew, A.L., et al., Modified release paracetamol overdose: a prospective observational study (ATOM-3). Clin Toxicol (Phila), 56:9, 810-819.

3. Bacon, T.H., et al., Analgesic efficacy of sustained release paracetamol in patients with osteoarthritis of the knee. British journal of clinical pharmacology, 2002. 53(6): p. 629-636.

4. Coulthard, P., et al., Pain control with paracetamol from a sustained release formulation and a standard release formulation after third molar surgery: a randomised controlled trial. Br Dent J, 2001. 191(6): p. 319-24.

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5. Cairney DG, Beckwith HK, Al-Hourani K, et al. Plasma paracetamol concentration at hospital presentation has a dose-dependent relationship with liver injury despite prompt treatment with intravenous acetylcysteine. Clin Toxicol. 2016;54:405–410.

6. Marks DJB, Dargan PI, Archer JRH, et al. Outcomes from massive paracetamol overdose: a retrospective observational study. Br J Clin Pharmacol. 2017;83:1263–1272.

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